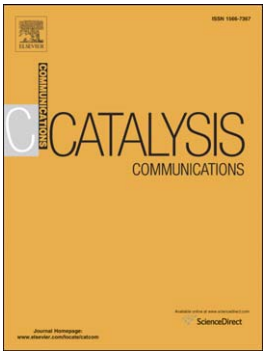

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PII: S1566-7367(12)00461-X
DOI: doi: 10.1016/j.catcom.2012.12.004
Reference: CATCOM 3356

To appear in: *Catalysis Communications*

Received date: 4 October 2012
Revised date: 3 December 2012
Accepted date: 4 December 2012

Please cite this article as: Audrey Decottignies, Aziz Fihri, Geoffrey Azemar, Florence Djedaini-Pilard, Christophe Len, Ligandless Suzuki-Miyaura reaction in neat water with or without native β-cyclodextrin as additive, *Catalysis Communications* (2012), doi: 10.1016/j.catcom.2012.12.004

Ligandless Suzuki-Miyaura reaction in neat water with or without native β-cyclodextrin as additive

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Abstract

Efficient green ligand-free Suzuki cross coupling in neat water was developed using low loading of catalyst (0.5 mol%) in neat water in presence or not of β-cyclodextrin (0.5 mol%) as additive at 25°C and 100°C respectively.

Keywords

β-cyclodextrin – Suzuki – aqueous catalysis

1. Introduction

Among the carbon-carbon bond-forming reactions using palladium: the Suzuki-Miyaura reaction, the Heck reaction, the Kumada reaction, the Stille reaction, the Negishi reaction, and the Sonogashira reaction, the palladium-catalyzed Suzuki coupling reaction has found wide applications in modern synthetic organic chemistry for the preparation of unsymmetrical biaryl compounds. The major advantages of the Suzuki-Miyaura reactions were the low-cost and commercial availability of a large number of boronic acids, as well as their nontoxic nature and stability to heat, air, and moisture. These reactions are usually carried out with palladium in the presence of auxiliary ligands using heterogeneous catalytic systems [1,2] and homogeneous catalytic systems [3]. Although the use of homogeneous catalysis provided environmental and economic problems in large scale-synthesis, it also afforded high reactivity, high turnover numbers, and milder reaction conditions. For example, a large variety of organic molecules was obtained in different scales from academic laboratories and industries such as Felbinac, Losartan, Boscalid, and Diovan.

Due to recent efforts in developing green chemistry and sustainable development for academic and industrial research, chemists have recently established a catalytic Suzuki-Miyaura protocol based on atom economy, less hazardous chemical syntheses, safer solvents and auxiliaries. In this respect, the Suzuki-Miyaura reaction was developed in safe, economical and environmentally benign aqueous media such as a cosolvent mixture in water [4] or neat water [5-8]. When the initial substrates were unsoluble in water, the most attractive choice was the use of surfactants [9] or inverse phase-transfer catalysts such as cyclodextrin [10-12] or calixarene [12] permitting the phase transfer of water-insoluble substrates.

In regard with the 12 green chemistry principles, the development of a ligandless protocol in an aqueous medium was recently reported [13-21]. Different mixtures such as EGME-water [13], PEG-water [14,15], ethanol-water [16], NMP-water [17,18], acetone-water [19], THF-water [20] and DMF-water [21] were successfully investigated. Only few ligandless Suzuki-Miyaura reactions in neat water with high yield were described. Starting from arylbenzoic acid and methyl arylbenzoate, the use of tetraalkylborate as a new type of borate source in presence of palladium charcoal-catalyzed Suzuki coupling reaction in water and without ligand could be achieve in good yield [22]. A reverse order of addition of reagents was developed starting from arylbenzoic acid and the corresponding methyl ester [23]. Recently, Mondal and Bora described an efficient protocol for palladium-catalyzed ligand-free Suzuki-Miyaura coupling in water with or without additive [24]. The primary advantage of the ligandless methodology is its ability to eliminate one reagent (e.g. phosphine derivatives).

This provides a less hazardous chemical syntheses and atom economy. The second key advantage is a marked improvement in reaction efficiency that allows for shorter reaction time, milder conditions and greater catalytic turnover.

To the best of our knowledge, only one report has described the Suzuki-Miyaura reaction in neat water using water unsoluble starting materials and ligand-free in the presence of modified α-cyclodextrin-capped palladium nanoparticles [25]. In this work, Antunes et al. used 2-hydroxypropyl-α-cyclodextrin as a reductant and capping agent for the Suzuki-Miyaura reaction and obtained different unsymmetrical biaryl compounds in high yields with significant catalytic activity [25]. Starting from modified α-cyclodextrin did not permit a phase transfer due to the little size of the hydrophobic internal cavity. In an attempt to expand the sustainable aspect of the Suzuki-Miyaura reaction, our group developed a successful ligand-free water-based method using a natural β-cyclodextrin (β-CD) promoter.

2. Experimental

2.1 General

All reactants were obtained from Acros Organics and were used as received without further purification. Solvents were purchased from Carlo Erba and were dried and freshly distilled under nitrogen. Water (deionized) was degassed by sparging with nitrogen. Chromatography was performed on a neutral silica gel. All reactions and workup procedures were performed under an inert atmosphere using conventional vacuum-line and glasswork techniques.

2.2. Characterization

NMR spectra of Suzuki coupling products were recorded on a Bruker instrument operating at 400.13 MHz for proton and 100.62 MHz for carbon. The qualitative and quantitative analysis of the reactants and products was performed by gas chromatography. Products were identified by a comparison with authentic samples. Conversion and GC yields were calculated with dodecane as an internal standard. NMR spectra for the complexation analysis were recorded on a Bruker instrument operating at 600.17 MHz.

An isothermal calorimeter (ITC_{200}, MicroCal Inc., USA) was used for determining the stoichiometry and the binding constant of the complex between different substrates and the cyclodextrin. Aliquots (0.5 µL to 2 µL) of titrant solution (11.1 to 38.3 mM) was added with syringe to titrate solution (200 µL, 0.38 to 2.83 mM) at 25 °C. Data analysis was carried out using Origin 7 software.

Samples for TEM analyses were prepared by depositing one drop of diluted nanoparticles aqueous dispersion on PVP-coated copper grids. After drying, the images were obtained by a Hitachi H 600 transmission electron microscopy (100 kV).

XPS studies were carried out in a Kratos Axis Ultra DLD spectrometer equipped with a monochromatic Al Ka-X-ray source (hν = 1486.6 eV) operating at 150 W, a multi-channel plate and delay line detector under 1.0 $x10^{-9}$ Torr vacuum. The survey and high-resolution spectra were collected at fixed analyzer pass energies of 160 and 20 eV, respectively. The instrument work function was calibrated to give an Au4f7/2 metallic gold binding energy of 83.95 eV. The spectrometer dispersion was adjusted to give a binding energy of 932.63 eV for metallic Cu 2p3/2. Samples were mounted in floating mode in order to avoid differential charging, charge neutralization was required for all samples. Binding energies were referenced to the C 1s binding energy of adventitious carbon contamination which was taken to be 284.80 eV [26,27]. The data were analyzed with commercially available software, CasaXPS. The individual peaks were fitted by a Gaussian (70%)-Lorentzian (30%) (GL30) function after Shirley type background subtraction.

2.3. Typical procedure for the Suzuki-Miyaura reaction

A 10 mL Schlenk flask was charged with bromoarene (0.25 mmol), phenylboronic acid (0.375 mmol, 1.5 eq), base (0.5 mmol, 2 eq), β-cyclodextrin ($1.25\ 10^{-3}$ mmol, 0.5 mol %). A solution of Pd ($1.25\ 10^{-3}$ mmol, 0.5 mol %) in water (2 mL) was added. The mixture was flushed with nitrogen, capped and placed in a pre-heated oil bath. The reaction mixture was stirred at the specified temperature for the specified time. Then the reaction mixture was extracted with ethyl acetate (3 x 3mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was analyzed by GC or purified by flash chromatography on silica gel.

3. Results and discussion

β-CDs are a family of cyclic oligosaccharides composed of α-(1→4)-linked D-glucopyranose units in $^4C_1$ chair conformation that have seven glucopyranose units. As a consequence of the non-modified β-CD structure, the molecule is hydrophilic and features a conical cavity that is essentially hydrophobic in nature with a size of the internal cavity permitting the phase transfer of water-unsoluble substrates. The best method consisted of obtaining an inclusion complex between a model initial substrate such as 4-bromacetophenone (**1**) and native β-CD

and not or weak inclusion complex between target compounds such as 4-acetylbiphenyl (**3**) and β-CD. NMR spectroscopy is one of the most reliable techniques for studying β-CD inclusion complexes. In our case, the ^{1}H NMR spectra of the native β-CD, β-CD-4-bromoacetophenone (**1**) mixture and β-CD-4-acetylbiphenyl (**3**) mixture were realized in D_2O. The mixture of the β-CD and 4-bromoacetophenone (**1**) showed apparent chemical shift changes of the β-CD cavity protons, H-3 and H-5. The H-3 and H-5 protons were shifted downfield in the range from 3.889 ppm; 3.782 ppm to 3.782 ppm; 3.661 ppm respectively. In contrast, the shifts of β-CD outside H-2 and H-4 could be neglected. The analysis of the ^{1}H NMR spectrum showed that the 4-bromoacetophenone (**1**) or a part of it was included into the β-CD cavity, thus, confirming the formation of an inclusion complex.

The T-ROESY spectrum of the β-CD (10 mM) and 4-bromoacetophenone (**1**) (10 mM) mixture showed that the protons peaks of the phenyl core (a, b) were highly correlated with the proton peaks of β-CD (H-3 and H-5). This confirmed that the phenyl ring was included into the β-CD cavity. In this case, two potent inclusion complexes could exist depending on the orientation of the 4-bromoacetophenone (**1**) inside the cavity; one with the bromide atom oriented in the primary face and the other with the bromide atom in the secondary face. The same experiments were realized with the replacement of 4-bromoacetophenone (**1**) by 4-acetylbiphenyl (**3**) in D_2O. The ^{1}H NMR spectrum of the mixture did not show apparent chemical shift change. To gain better insight into the complexation phenomena, experiments were also conducted with Isothermal Titration Calorimetry (ITC) [28].

Figure 1 describes the ITC enthalpogram for addition of β-CD with 4-bromoacetophenone (**1**) in pure water at 25°C. Negative peaks were observed for each addition as a consequence of the formation of inclusion complex. The intensities decreased as such association weakens as the host concentration inside the cell increased. The fit of these data to the theoretical model allowed the determination of the thermodynamic parameters. The stoichiometry was 1:1 and association constant was equal to 634 (± 19) M^{-1} at 25°C. In our hands, the same experiments performed with 4-acetylbiphenyl (**3**) used as guest in pure water failed. However in a mixture of water and acetone (50:50), a low value of inclusion constant could be obtained (155 ± 36 M^{-1} at 25°C).

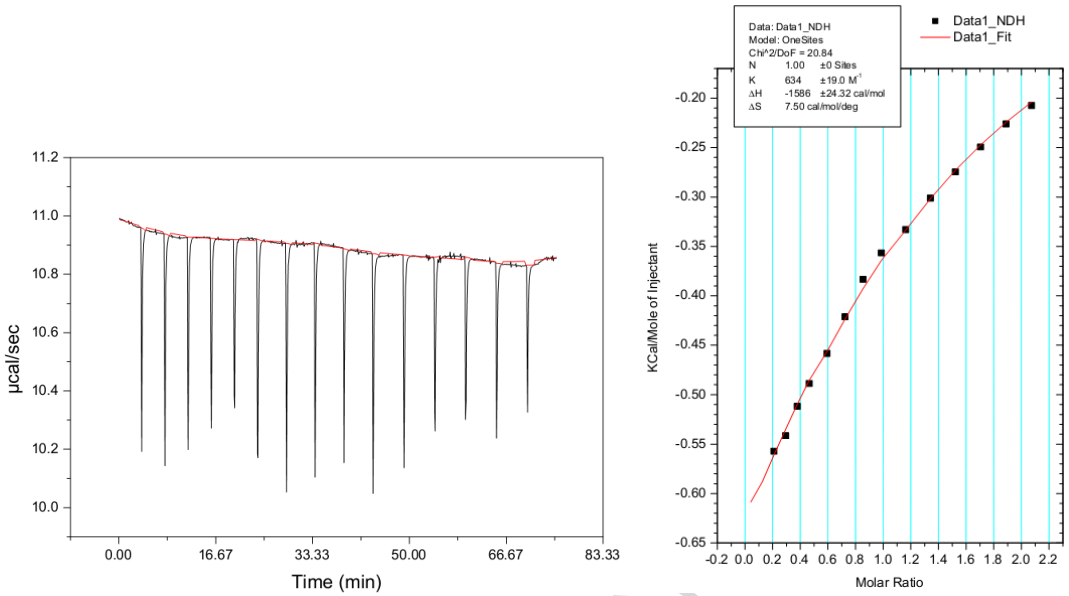


Fig. 1. Representative observed heats (left part) and corresponding binding isotherm (right part) for ITC complexation experiments between native β-CD and 4-bromoacetophenone (**1**). Solid line represents the best theoretical fit to experimental points.

Even if the structure of compound **3** could form an inclusion complex the association constant was low in our conditions. These results demonstrated that native β-CD could be used as a mass transfer promoter for the initial compound in the Suzuki reaction. The results also showed that the target hydrophobic biphenyl core could be easily extracted.

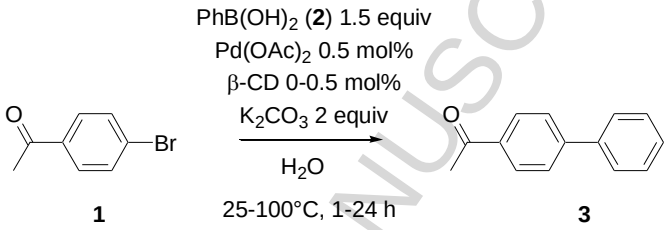
In the first set of experiments, the reaction of 4-bromoacetophenone (**1**) (1 equiv) with phenylboronic acid (**2**) (1.5 equiv) was carried out as a model reaction in sole water at 100°C with K_2CO_3 (2 equiv) using $Pd(OAc)_2$ (0.5 mol%) as the catalyst and native β-CD (0.5 mol%) (Table 1, entry 1). It was notable that in the literature the amount of β-CD was higher and often similar with the concentration of the starting material.

In our conditions, the target aryl analogue **3** was obtained with a 97% yield after 1 hour. In order to know the potent role of mass transfer of the native β-CD, Suzuki coupling was conducted without β-CD and the target 4-acetylbiphenyl compound **3** was obtained after 1 hour with a 87% yield (Table 1, entry 1). A longer reaction time (2 hours *vs* 1 hour) did not increase the yield of biaryl compound **3** (Table 1, entry 2). Lowering the temperature from 100°C to 25°C in the presence of β-CD did not decrease the yield of the target biphenyl analogue **3** but extended reaction time (24 hours *vs* 1 hour) (Table 1, entry 3). At 100°C, the yields of the biaryl derivatives were higher than 87% (Table 1, entries 1 and 2) and the use of β-CD permitted to increase the yield by 10% (Table 1, entries 1 and 2). At 25°C, the

difference in yield was higher than at 100°C (94% *vs* 63%, Δ = 31%) (Table 1, entry 3). The inclusion complex between native β-CD and compound **1** was more stable at 25°C than at 100°C affording a better reactivity for the Suzuki-Miyaura coupling in neat water.

Table 1

Variation of temperature with and without β-CD (0.5 mol%) for the Suzuki-Miyaura coupling starting from 4-bromoacetophenone (**1**).



Entry	Temp. (°C)	Time (h)	Yield[a] (%)
1	100	1	97[b] (87)[c]
2	100	2	99[b] (88)[c]
3	25	24	94[b] (63)[c]

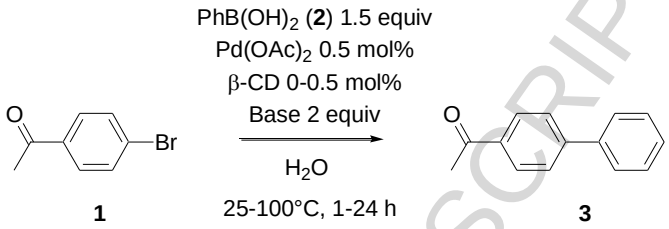
[a] Determined by GC methods. Products were compared with authentic samples. [b] Reaction conditions: **1** (0.25 mmol), $PhB(OH)_2$ (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25-100°C, 1-24 h. [c] Reaction conditions: **1** (0.25 mmol), $PhB(OH)_2$ (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25-100°C, 1-24 h.

Different bases, including K_2CO_3, Na_2CO_3, Cs_2CO_3, CsF, K_3PO_4, NaOH, KOH and Et_3N were tested with the optimized conditions described in Table 2. On the one hand, at 100°C for 1 hour, with or without β-CD, the different bases afforded the target biaryl compound **3** in good to excellent yield (Table 2). When CsF was used, the yield of the Suzuki-Miyaura product was lower (Table 2, entry 7). On the other hand, at 25°C for 24 hours, the bases had dramatic effects on the yields of the cross-coupling product **3** (from 7% to 99%). At 25°C and in the presence of β-CD (0.5 mol%), only K_2CO_3, Na_2CO_3, Cs_2CO_3, K_3PO_4, NaOH and KOH gave the biaryl structure **3** in good yield. At 25°C and without the presence of β-CD, the target 4-acetylbiphenyl compound **3** was obtained in a lower yield. This was particularly

evident with CsF, K_3PO_4 and Et_3N (Table 2, entries 8, 10 and 16). Considering the economical and environmental advantages, K_2CO_3 was chosen as the base.

Table 2

Variation of the nature of base for the Suzuki-Miyaura coupling starting from 4-bromoacetophenone (**1**) with or without β-CD.



Entry	Base (2 equiv)	Temp. (°C)	Time (h)	Yield[a] (%)
1	K_2CO_3	100	1	97[b] (87)[c]
2	K_2CO_3	25	24	94[b] (63)[c]
3	Na_2CO_3	100	1	99[b] (97)[c]
4	Na_2CO_3	25	24	99[b] (86)[c]
5	Cs_2CO_3	100	1	93[b] (85)[c]
6	Cs_2CO_3	25	24	99[b] (81)[c]
7	CsF	100	1	75[b] (72)[c]
8	CsF	25	24	43[b] (32)[c]
9	K_3PO_4	100	1	90[b] (86)[c]
10	K_3PO_4	25	24	96[b] (29)[c]
11	NaOH	100	1	95[b] (91)[c]
12	NaOH	25	24	99[b] (94)[c]
13	KOH	100	1	85[b] (83)[c]
14	KOH	25	24	94[b] (93)[c]
15	Et_3N	100	1	95[b] (94)[c]
16	Et_3N	25	24	60[b] (7)[c]

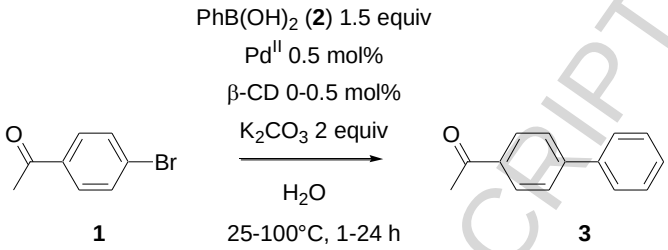
[a] Determined by GC methods. Products were compared with authentic samples. [b] Reaction conditions: **1** (0.25 mmol), $PhB(OH)_2$ (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD

(0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25-100°C, 1-24 h. [c] Reaction conditions: **1** (0.25 mmol), $PhB(OH)_2$ (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25-100°C, 1-24 h.

In search of a more efficient catalyst, the next step consisted of examining different Pd^{II}-based species. Palladium sources were screened by using the same amount of catalyst (0.5 mol% of either PdI_2, $PdCl_2$, Na_2PdCl_4, $[Pd(C_3H_5)Cl]_2$ or $Pd(PhCN)_2Cl_2$), and by varying the concentration of native β-CD (0 or 0.5 mol%), as well as the temperature and time (25°C for 24 hours and 100°C for 1 hour). Even though all the palladium derivatives promoted the formation of biaryl analogues, none of these palladium derivatives was as good as $Pd(OAc)_2$ for the four methods tested (table 3). It was notable that $PdCl_2$ permitted the Suzuky-Miyaura coupling with a 96% yield in the presence of β-CD (0.5 mol%) at 25°C for 24 hours (table 3, entry 6). $Pd(PhCN)_2Cl_2$ also afforded the biaryl compound **3** in 98% yield in the presence of β-CD (0.5 mol%) at 100°C for 1 hour (table 3, entry 11).

Table 3

Variation of the nature of Pd^{II}-based species for the Suzuki-Miyaura coupling starting from 4-bromoacetophenone (**1**) with or without β-CD.



Entry	PdII based species	Amount (mol%)	Temp. (°C)	Time (h)	Yield[a] (%)
1	$Pd(OAc)_2$	0.5	100	1	97[b] (87)[c]
2	$Pd(OAc)_2$	0.5	25	24	94[b] (63)[c]
3	PdI_2	0.5	100	1	64[b] (61)[c]
4	PdI_2	0.5	25	24	4[b] (1)[c]
5	$PdCl_2$	0.5	100	1	93[b] (85)[c]
6	$PdCl_2$	0.5	25	24	96[b] (14)[c]
7	Na_2PdCl_4	0.5	100	1	91[b] (78)[c]
8	Na_2PdCl_4	0.5	25	24	25[b] (8)[c]
9	$[Pd(C_3H_5)Cl]_2$	0.5	100	1	39[b] (28)[c]
10	$[Pd(C_3H_5)Cl]_2$	0.5	25	24	1[b] (1)[c]
11	$Pd(PhCN)_2Cl_2$	0.5	100	1	98[b] (77)[c]
12	$Pd(PhCN)_2Cl_2$	0.5	25	24	68[b] (8)[c]

[a] Determined by GC methods. Products were compared with authentic samples. [b] Reaction conditions: **1** (0.25 mmol), $PhB(OH)_2$ (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25-100°C, 1-24 h. [c] Reaction conditions: **1** (0.25 mmol), $PhB(OH)_2$ (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25-100°C, 1-24 h.

As a result of the previous experiments, four methods were defined in order to establish different optimized reaction conditions (variations in the nature of the base and palladium source, the temperature, the time and the presence or absence of the mass transfer promoter β-CD) (Table 4).

Table 4

Four optimized reaction conditions for the Suzuki-Miyaura coupling starting from aryl bromide with or without β-CD.

Entry	Amount of β-CD (mol%)	Temp. (°C)	Time (h)
A[a]	0.5	100	1
B[b]	-	100	1
C[c]	0.5	25	24
D[d]	-	25	24

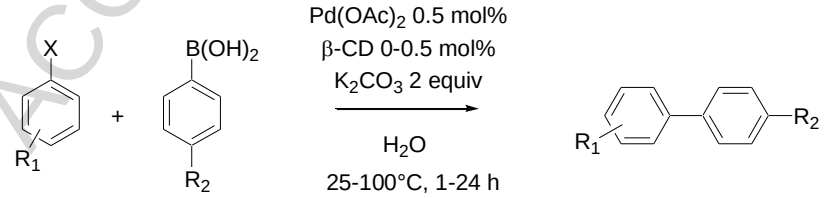
[a] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), Pd^{II} (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 100°C, 1 h.
[b] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), Pd^{II} (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 100°C, 1 h.
[c] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), Pd^{II} (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25°C, 24 h.
[d] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), Pd^{II} (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25°C, 24 h.

Using these four methods (Table 4), a range of arylboronic acids with different electronic and steric demands in the Suzuki-Miyaura reaction were screened. Arylbromides with various functional groups efficiently reacted with boronic acids (Table 5) to give the Suzuki-Miyaura product with good to excellent yield. Using methods A and B at 100°C for 1 hour, the Suzuki-Miyaura products were obtained with higher yields than those that used methods C and D at 25°C for 24 hours, respectively, except for the 4-bromobenzaldehyde without β-CD (Table 5, entries 5 and 6). The presence of native β-CD often gave better yields for the Suzuki-Miyaura coupling than the reaction without the mass transfer promoter (Table 5). The yields should be

a function of the solubility of the starting material and reagents in water. Nevertheless, the presence of an electron withdrawing group in the 4- position of the aryl bromide afforded the biaryl derivatives in high yields using methods A and C (Table 5, entries 1, 2 and 5-8). However, the presence of a donating group often gave weaker yields (Table 5, entries 4, 9 and 10) with the exception of the methoxy group at 100°C (Table 5, entry 3). The substitution of phenylboronic acid (Table 5, entries 1, 2, 5 and 6) by 4-acetylphenylboronic acid (Table 5, entries 13-16) gave the target biaryl compounds in lower yields (46-83% *vs* 90-99%). Our methodology did not permit to obtain the biaryl compound starting from aryl chlorides (Table 5, entries 11 and 12). Starting from 2-bromotoluene and 2-bromoanisole in the presence of phenylboronic acid, the use of methods A-D permitted the synthesis of the target biaryl derivatives in low yields (Table 5, entries 17-20). In our conditions, the steric hindrance did not allow the C-C coupling with yields higher than 22%. In addition, the use of 2-bromotoluene led to an unseparable mixture of the target compound and biphenyl obtained by homocoupling. In our hands, the best result for the synthesis of 2-methylbiphenyl was 19% yield and determined by NMR estimation.

Table 5

Suzuki-Miyaura coupling of various aryl bromides with arylboronic acids with or without β-CD.



Entry	X	R1	R2	Yield[a] (%)

1	Br	4-$(CO)CH_3$	H	95[b] (84)[c]
2	Br	4-$(CO)CH_3$	H	90[d] (59)[e]
3	Br	4-OCH_3	H	97[b] (68)[c]
4	Br	4-OCH_3	H	22[d] (10)[e]
5	Br	4-CHO	H	99[b] (55)[c]
6	Br	4-CHO	H	90[d] (84)[e]
7	Br	4-CN	H	91[b] (76)[c]
8	Br	4-CN	H	84[d] (34)[e]
9	Br	4-NH_2	H	60[b] (51)[c]
10	Br	4-NH_2	H	8[d] (3)[e]
11	Cl	4-$(CO)CH_3$	H	2[b] (1)[c]
12	Cl	4-$(CO)CH_3$	H	1[d] (1)[e]
13	Br	4-$(CO)CH_3$	4-$(CO)CH_3$	62[b] (58)[c]
14	Br	4-$(CO)CH_3$	4-$(CO)CH_3$	46[d] (42)[e]
15	Br	4-CHO	4-$(CO)CH_3$	80[b] (78)[c]
16	Br	4-CHO	4-$(CO)CH_3$	83[d] (36)[e]
17	Br	2-CH_3	H	19[b,f] (10)[c,f]
18	Br	2-CH_3	H	14[d,f] (7)[e,f]
19	Br	2-OCH_3	H	22[b] (12)[c]
20	Br	2-OCH_3	H	19[d] (7)[e]

[a] Isolated yields.

[b] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 100°C, 1 h.

[c] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 100°C, 1 h.

[d] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25°C, 24 h.

[e] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$

(0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25°C, 24 h. [f] The yield was determined by NMR estimations.

Starting from 2-bromothiophene and 2-bromonaphthalene in the presence of phenylboronic acid, the use of methods A-D afforded the target biaryl compounds (Table 6). In all cases, the presence of native β-CD permitted to obtain the target biaryl compounds in better yield (at 100°C, 41 *vs* 18% and at 25°C 61 *vs* 1%) (Table 6). It was notable that, using method A, 2-bromonaphthalene did not afford the higher yield (Table 6, entry 1) as observed for the other aryl bromide (Table 5). One plausible explanation was that the inclusion complex between native β-CD and 2-bromonaphthalene was more stable at 25°C than at 100°C affording a better reactivity for the Suzuki-Miyaura coupling in neat water. 2-Bromothiophene gave no coupling product due to a potent instability in water (Table 6, entries 3 and 4). Moreover, it should be possible that a potent interaction between the sulphur atom and the palladium complex afforded a desactivation effect on the rate of the reaction.

Table 6

Suzuki-Miyaura coupling starting from 2-thiophene and 2-bromonaphthalene with or without β-CD.

Entry	R1	Yield[a] (%)
1	2-naphthyl	41[b] (18)[c]
2	2-naphthyl	62[d] (1)[e]
3	2-thienyl	3[b] (0)[c]
4	2-thienyl	2[d] (1)[e]

[a] Isolated yields. [b] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 100°C, 1 h. [c] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 100°C, 1 h. [d] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), β-CD (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25°C, 24 h.

[e] Reaction conditions: aryl bromide (0.25 mmol), arylboronic acid (0.375 mmol), $Pd(OAc)_2$ (0.5 mol%), K_2CO_3 (0.50 mmol), water (2 mL), 25°C, 24 h.

In order to study the variations of the size of the internal cavity and the hydrophily of the oligosaccharides, the replacement of β-CD by α-CD, γ-CD, DIMEB of β-CD, per-methylated α-CD and per-methylated γ-CD was effected using methods A and C. In our hand, none of the CD analogues gave the Suzuki-Miyaura coupling products with yields higher than those obtained with native β-CD. Moreover, the replacement of cyclodextrin by D-glucose in different concentrations (0.5 mol% to 3.5 mol%) did not permit an increase in the yield of the target compound.

The addition of phenylboronic acid (**2**, 0.37 mM) and $Pd(OAc)_2$ (0.5mol%) in neat water as solvent afforded spherical nanoparticules, 4.63-8.25 nm in size (Figure 2). Similar nanoparticules were observed during the Suzuki-Miyaura reactions. In our study, the dispersibility of nanoparticules in water was neglected.

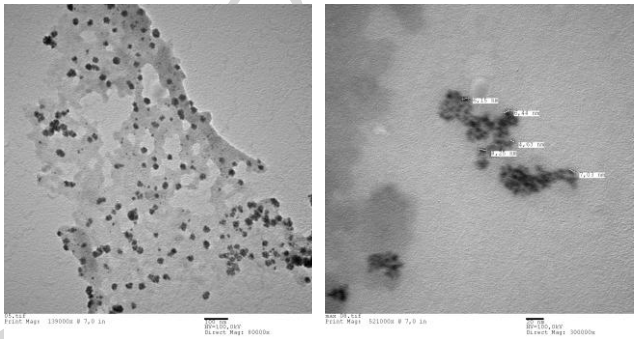


Fig. 2. TEM micrographs obtained from a mixture of phenylboronic acid (**2**, 0.37 mM) and $Pd(OAc)_2$ (0.5mol%) in H_2O at 25°C.

The X-ray photoelectron spectroscopy (XPS) analysis of the nanoparticules obtained by: (i) addition of phenylboronic acid (**2**, 0.37 mM) and $Pd(OAc)_2$ (0.5mol%) in water; (ii) after our Suzuki-Miyaura methods (methods A-D) revealed that among the palladium species detected, Pd(II) and Pd(0), the latter was formed as a major phase.

4. Conclusion

In summary, the Suzuki-Miyaura reaction was used to obtain a large range of commercial compound with high added value. From the view point of green chemistry, different methods have been developed to produce biaryl derivatives with various steric and electronic substituents in good yields. Our optimization furnished four efficient methods for the ligandless Suzuki-Miyaura reaction using $Pd(OAc)_2$ as a catalyst (0.5 mol%) in neat water at 25°C and 100°C : two methods without additive and two methods with the presence of low amount of native β-CD (0.5 mol%). In the literature the amount of β-CD was higher and often similar with the concentration of the starting material. In our hands, the use of native β-CD often gave better yield than the reaction without the mass transfer promoter. Starting from hindered aryl bromide such as 2-bromonaphthalene, the presence of native β-CD permitted to furnish the target compound with a significant enhancement of the yield (at 100°C, 41 *vs* 18% and at 25°C 61 *vs* 1%). Using our methodology, $Pd(OAc)_2$ is reduced *in situ* to form catalytically Pd(0) species in nanoparticle forms and the catalytic system cannot be recycled. To the best of our knowledge, this is the first time that the Suzuki-Miyaura reaction has been performed under such green conditions.

Acknowledgements

Authors are grateful to the Région Picardie and Europe (FEDER) for their financial support.

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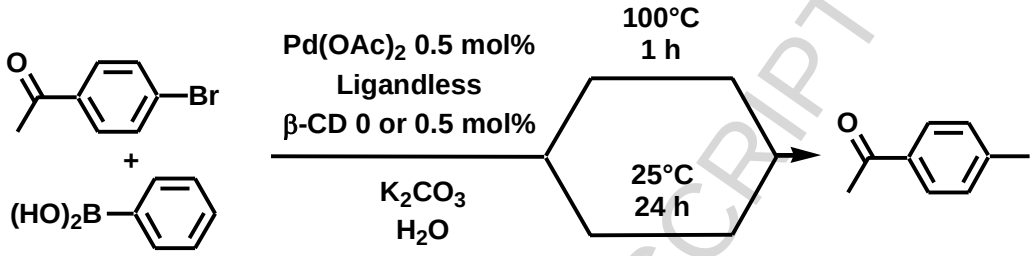
Graphical abstract



Highlights

Suzuki cross-coupling reactions using ligand-free palladium $Pd(OAc)_2$

Suzuki cross-coupling was performed in water

The method was applied successfully to a number of brom substituted reactants

The presence of low amount of native b-CD (0.5 mol%)